REMARKS

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

Date October 16, 2002

By Jayme A. Hobbs
Reg. No. 34,485

FOLEY & LARDNER
Customer Number: 22428
22428
PATENT TRADEMARK OFFICE
Telephone: (202) 672-5475
Facsimile: (202) 672-5399

Beth A. Burrous
Attorney for Applicant
Registration No. 35,087

MARKED UP VERSION ATTACHED TO AMENDMENT IN

SERIAL NO. 10/049,429

Marked up version of the paragraph starting at page 27, lines 11-12 is below:

FIG. 4 provides a sequence alignment of the D2-D3 region of human FGF1, FGF2, FGF3 and FGF4 **(SEQ ID NOS 1-4, respectively)**.

Marked up version of the paragraph starting at page 29, lines 1-2 is below:

Figure 15 shows Structure-based sequence alignment of the ligand binding domains of D2 and D2-D3 linker of human FGF receptors **(SEQ ID NOS 5-8, respectively)**.

Marked up version of the paragraph starting at page 29, lines 3-4 is below:

Figure 16 shows Structure-based sequence alignment of the ligand binding domains of D3 of human FGF receptors **(SEQ ID NOS 9-16, respectively)**.

Marked up version of the paragraph starting at page 29, lines 5-21 is below:

Figure 17 shows structure-based sequence alignment of FGFs **(SEQ ID NOS 17-35, respectively, in order of appearance)** performed using the CLUSTALW program (Thompson et al., Nucleic Acids Res. 22, 4673-4680 (1994)). All of the FGFs used in this alignment are from human, with the exception of FGF15, for which only the chicken sequence is available. The secondary structure assignment is according to the published nomenclature, with the beta strands labeled from 1 through 12 (Faham et al., Curr. Opin. Struct. Biol. 8, 578-586 (1998)). The location and the length of the beta strands are shown on the top of the sequence alignment. FGF residues are colored with respect to the region on FGFR with which they interact: FGF residues that interact with D2 are colored green, residues that interact with the linker region are colored gray, and residues that interact with D3 are colored cyan. FGF residues that interact with the

betaC'-betaE segment in D3 are colored red. A period indicates sequence identity to FGF2. A dash represents a gap introduced to optimize the alignment. A tilde at the C-terminus of FGF indicates that there are additional sequences down stream to the last amino acid shown. A star indicates that numbering does not start at the initiation methionine. Residue numbering for FGF2 is according to Springer et al., J. Biol. Chem. 269, 26879-26884 (1994). Residue numbering for FGF1 is according to Zhu et al., Science 251, 90-93 (1991). A checkmark indicates FGF residues that have been shown by mutagenesis to be important for receptor binding.

Marked up version of the paragraph starting at page 30, lines 4-6 is below:

Figure 20 depicts the sequence alignment based on secondary structures of SCF, M-CSF and IL-5 **(SEQ ID NOS 36-44, respectively, in order of appearance)**. Secondary structure assignments for M-CSF and IL-5 are from PDB databank. beta-Strands are yellow and helices are marked bright green.

Marked up version of the paragraph starting at page 30, lines 25-28 is below:

Figure 25 shows sequence alignments of human, rat, mouse, dog and pig SCFs **(SEQ ID NOS 45-49, respectively)**. Residues of the acidic patch are colored red and residues of the two basic patches are colored blue. Stars mark amino acid residues that are altered in rodents. The secondary structures are marked below the sequences with 'H' representing helices and 'E' representing beta strands.

Marked up version of the paragraph starting at page 56, line 20 is below:

In the crystal structures of the receptor-bound FGF1 and FGF2, residues upstream of ß1 are found to be disordered (Eriksson et al., 1991; Blaber et al., 1996; Zhu et al., 1991). However, in the crystal structures of the receptor-bound FGF1 and FGF2 these residues are ordered and in proximity to D3 of FGFRs (Fig. 12 and 14). In the FGF2-FGFR2 structure, the side chain of Phe17 is located in a shallow hydrophobic pocket in D3 that is formed by Pro286, Ile288 and Val280 (Fig. 12). Moreover, Phe17

forms several hydrogen bonds via backbone atoms with Ser282 and Gln285 in D3. Lys18 in FGF2 also makes several hydrogen bonds with the side chains of Lys279 and Glu325 and with the backbone of Val280 in D3 (Fig. 12). In agreement with these structural observations, it has been shown that a synthetic peptide consisting of residues 13-18 of FGF2 (prior to ß1) competes with the binding of FGF2 to FGFR (Yayon et al., 1993). The amino acids ^{7}NYKKPKL^{13} **(SEQ ID NO: 202)** located at the junction between the N-terminal segment and ß1 in FGF1 have been proposed to signal the nuclear accumulation of FGF1 that occurs during sustained exposure of cells to FGF1 (Imamura et al., 1990). In the FGF1-FGFRI structure, Tyr8 located in this amino acid stretch inserts into a shallow hydrophobic pocket formed by the side chains of Val279, Pro285 and Ile287. The structural data described herein provide a direct role for this region in receptor binding. Deletion mutagenesis experiments support our structural finding. FGFR1 molecules lacking this amino acid stretch have a 250-fold reduced ability to bind FGFR (Imamura et al., 1990). A structure-based sequence alignment of FGFs reveals significant sequence diversity in the segment upstream of ß1 in FGFs, suggesting that this region may also play a role in determining FGF binding specificity (Fig. 17).

Marked up version of the paragraph starting at page 92, lines 13-17 is below:

Table 3 provides the atomic structural coordinates of the FGF2/FGFR2 complex dimer. The structure of the FGFR2/FGF2 complex has been described in Plotnikov et al., *Cell 101*, 413-424 (2000) and the coordinates for the FGFR2/FGF2 complex are available on the internet through the Protein Data Bank (assigned Protein Data Bank ID code 1EV2), the disclosures of which are herein incorporated by reference. **Table 3 contains sequence data that meets the requirements for inclusion into a Sequence Listing. Sequences SEQRES1A (p. 292) through SEQRES17H (p. 294) have been assigned SEQ ID NOS 50-157, respectively, in order of appearance, with the exceptions of nonqualifying sequences SEQRES11A, SEQRES11B, SEQRES11C, and SEQRES11D.**

Marked up v rsion of the paragraph starting at page 95, lines 17-28 is below:

The structure was determined by using anomalous scattering differences of samarium ions in the crystal at two wavelengths and refined to 2.3 Å (Table 4). There are four molecules in each asymmetric unit and the initial experimental electron density clearly showed the four-helix bundle and two beta strands in the molecules. The connecting loops, as well as the N-terminal and C-terminal regions, were built from 2Fo-Fc maps. Table 4 gives the statistics of the final model, which contains 120 solvent molecules, four samarium ions, two calcium ions and one Tris molecule. The structure of the human stem cell factor homodimer has been described in Zhang et al., Proc.Nat.Acad.Sci. *97(14)*, 7732-7737 (2000) and the coordinates for the human SCF dimer are available on the internet through the Protein Data Bank (Protein Data Bank ID code 1EXZ) at http://www.rcsb.org/pdb/cgi/explore.cgi?pid=17825967231743&pdbId=1EXZ, the disclosures of which are herein incorporated by reference. **Table 4 contains sequence data that meet the requirements for inclusion into a Sequence Listing. SEQRES1A through SEQRES11D (p. 460) have been assigned SEQ ID NOS 158-201, respectively, in order of appearance.**